malonic Ester (30) with 12.—A mixture of 5 g. of **30**[18] and 2.76 g. of **12** were mixed in 10 ml. of diglyme. No temperature rise was noted. After 24 hr. at room temperature, the reaction was diluted with water and unchanged **30** recovered, m.p. 58–61°.

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(18) C. D. Hurd and L. T. Sherwood, *J. Org. Chem.*, **13**, 471 (1948).

Acknowledgment.—The authors wish to express their sincere appreciation to Miss Natalie Cahoon and co-workers for spectra determinations and to Mr. George Robertson and co-workers for analytical results.

Reactions of Mercaptoamines. I. With Isocyanates and Isothiocyanates[1]

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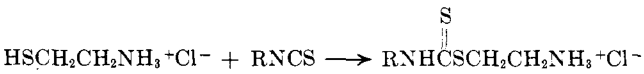
Received May 3, 1963

Isothiocyanates reacted with 2-mercaptoethylamine hydrochloride to give S-substituted products, the hydrochlorides of S-2-aminoethyl N-alkyldithiocarbamates. With free 2-mercaptoethylamine, one mole of phenyl isothiocyanate gave the N-substituted product, 1-(2-mercaptoethyl)-3-phenyl-2-thiourea, and two moles gave the N,S-disubstituted product. All aliphatic isothiocyanates gave disubstituted products, the 1-[2-(N-alkyldithiocarbamoyl)ethyl]-3-alkyl-2-thioureas, regardless of the relative amount of isothiocyanate. The disubstituted products were cleaved by silver nitrate to one mole of the isothiocyanate and the silver mercaptide of the 1-(2-mercaptoethyl)-3-alkyl-2-thiourea, from which the free thiourea was obtained by treatment with sodium sulfide. Isocyanates, regardless of relative amount, reacted with 2-mercaptoethylamine to give the N,S-disubstituted products. Cleavage with silver nitrate afforded the 1-(2-mercaptoethyl)-3-alkylureas.

The behavior of isocyanates and isothiocyanates toward active hydrogen compounds has been studied since the earliest days of organic chemistry, and it is well known that both react vigorously with amines, and that isocyanates also react, somewhat less vigorously, with alcohols and water.[2] In contrast, isothiocyanates are so relatively unreactive toward hydroxyl-containing compounds that aqueous media often are used in their preparation,[3] and their reaction with hydroxyalkyl amines gives hydroxyalkyl thioureas.[4] Both isocyanates and isothiocyanates have been reported to react with thiols,[5] but there is no evidence to indicate how readily these reactions proceed relative to reaction with the amino group. Consequently there was no *a priori* way of predicting how compounds containing both the thiol and the amino function would react with isocyanates and isothiocyanates. This question became of importance in connection with the proposed preparation of a number of 2-mercaptoethyl ureas and thioureas for testing as radioprotective drugs, and an examination of the reaction of 2-mercaptoethylamine with isocyanates and isothiocyanates was undertaken.

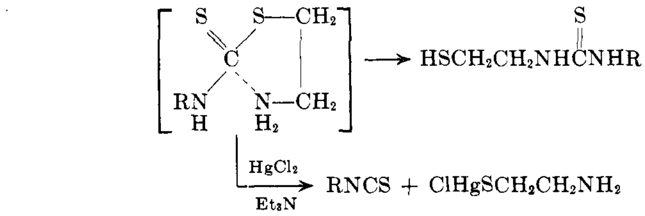
The reaction with isothiocyanates was studied first, since there seemed to be a better chance of directing this reaction preferentially to one or the other functions of the 2-mercaptoethylamine molecule. When a solution of 2-mercaptoethylamine hydrochloride in ethanol (pH 5 to Hydrion test paper) was treated with phenyl or *n*-butyl isothiocyanate, there was no reaction. However, when a few drops of aqueous sodium hydroxide were added, raising the pH to 6–6.5, vigorous exothermic reaction took place and solid products crystallized. Analysis indicated that these products



$$HSCH_2CH_2NH_3^+Cl^- + RNCS \longrightarrow RNH\overset{S}{\overset{\|}{C}}SCH_2CH_2NH_3^+Cl^-$$

were the result of reaction at the thiol function, that is, that they were the hydrochlorides of S-2-aminoethyl N-phenyldithiocarbamate (72% yield) and N-*n*-butyldithiocarbamate (74%), respectively. This structure assignment was confirmed by their chemical behavior and by the fact that 2-dimethylaminoethanethiol hydrochloride, which can react only at the thiol function, reacted vigorously with phenyl isothiocyanate at pH 6. Treatment of an aqueous solution of the product with base gave free S-(2-dimethylamino)ethyl N-phenyldithiocarbamate in 66% yield.

The dithiocarbamates derived from 2-mercaptoethylamine were much less stable. The hydrochlorides dissolved in water to give clear solutions, but the solutions underwent rapid hydrolysis. In a few minutes cloudiness appeared, and the characteristic odor of the parent isothiocyanate became strongly noticeable. When the hydrochlorides were treated with an equivalent of weak base, they rearranged to the corresponding N-substituted derivatives of 2-mercaptoethylamine, giving



1-(2-mercaptoethyl)-3-phenyl-2-thiourea (77%) and somewhat impure 1-(2-mercaptoethyl)-3-*n*-butyl-2-thiourea (77%). This rearrangement appears to be exactly analogous to the known rearrangement of S-acyl 2-mercaptoethylamine derivatives.[6,7] As a preparative route to 2-mercaptoethylthioureas this reaction was less satisfactory than other techniques to be de-

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(1) This work was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Contract No. DA-49-193-MD-2174.

(2) I. D. Morton and E. Hoggarth, "Chemistry of Carbon Compounds," Vol. IB, E. H. Rodd, Ed., Elsevier Publishing Co., Amsterdam, The Netherlands, 1952, p. 939.

(3) M. L. Moore and F. S. Crossley, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 599.

(4) F. B. Dains, R. Q. Brewster, I. L. Malm, A. W. Miller, R. V. Maneval, and J. A. Sultzaberger, *J. Am. Chem. Soc.*, **47**, 1981 (1925).

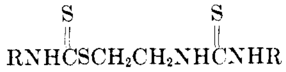
(5) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. IV, Chemical Publishing Co., Inc., New York, N. Y., 1962, pp. 201 and 238.

(6) J. Baddiley and E. M. Thain, *J. Chem. Soc.*, 3425 (1951).

(7) T. Wieland and E. Bokelmann, *Ann.*, **576**, 20 (1952).

TABLE I

1-[2-(N-ALKYLDITHIOCARBAMOYL)ETHYL-3-ALKYL]-2-THIOUREAS

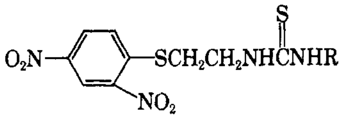


$$\mathrm{RNH\overset{S}{\overset{\|}{C}}SCH_2CH_2NH\overset{S}{\overset{\|}{C}}NHR}$$

R	Yield, %	M.p., °C.	Calcd. C	Calcd. H	Calcd. N	Calcd. S	Found C	Found H	Found N	Found S
CH_3	74	136–138	32.26	5.86	18.81	43.06	32.49	5.92	18.69	43.24
C_2H_5	78	124.5–126.5	38.21	6.82	16.71	38.25	38.10	6.85	16.71	38.11
i-C_3H_7	87	128–129.5	42.97	7.58	15.04	34.42	43.04	7.69	14.88	34.25
n-C_4H_9	100	98–101.5	46.87	8.19	13.66	31.28	47.02	8.10	13.57	31.46
n-C_7H_{15}	99	91–92.5	55.19	9.52	10.73	24.56	55.11	9.49	10.78	24.59
C_6H_5	98	150.5–152.5	55.30	4.93	12.09	27.68	55.15	5.02	11.95	27.85

TABLE II

2,4-DINITROPHENYL SULFIDE DERIVATIVES OF 1-ALKYL-3-(2-MERCAPTOETHYL)-2-THIOUREAS



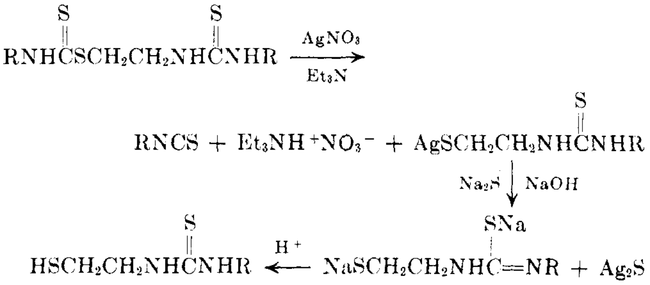
R	Yield, % Thiourea	Yield, % Deriv.	M.p., °C.	Calcd. C	Calcd. H	Calcd. N	Calcd. S	Found C	Found H	Found N	Found S
CH_3	57	53	158–160	37.97	3.83	17.71	20.27	38.05	3.89	17.68	20.38
C_2H_5	58	73	142.5–145	39.99	4.27	16.96	19.41	40.02	4.30	16.83	19.12
n-C_4H_9	47	69	135–137	43.56	5.06	15.63	17.89	43.66	4.88	15.50	18.00
n-C_7H_{15}	66	90	145.5–146.5	47.98	6.04	13.99	16.01	48.17	6.16	14.04	15.88

scribed later. The free dithiocarbamates apparently required a finite period to rearrange, for when a suspension of S-2-aminoethyl N-phenyldithiocarbamate hydrochloride in acetone was treated with triethylamine and then immediately with a solution of mercuric chloride in acetone, phenyl isothiocyanate was obtained in 41% yield. This could have been obtained only from the dithiocarbamate by metal ion-assisted mercaptan elimination.[8] Regeneration of the isothiocyanate in this reaction constitutes excellent proof that the structure of the dithiocarbamate was correctly assigned.

When free 2-mercaptoethylamine was treated with an equimolar amount of phenyl isothiocyanate, reaction took place at the amino function, and 1-(2-mercaptoethyl)-3-phenyl-2-thiourea was obtained in 91% yield. It was expected that this reaction could be extended to the aliphatic isothiocyanates and that a series of 2-mercaptoethylthioureas could be prepared easily. However, aliphatic isothiocyanates invariably reacted at both functions of 2-mercaptoethylamine even when present in deficient amount, and the products were the 1-[2-(N-alkyldithiocarbamoyl)ethyl]-3-alkyl-2-thioureas. Products of this type were prepared from a number of aliphatic isothiocyanates and from phenyl isothiocyanate when it reacted with 2-mercaptoethylamine in a 2:1 ratio. The properties of these materials are summarized in Table I. The excellent yields reported were obtained with a 2:1 isothiocyanate to 2-mercaptoethylamine mole ratio.

$$\mathrm{HSCH_2CH_2NH_2 + RNCS \longrightarrow RNH\overset{S}{\overset{\|}{C}}SCH_2CH_2NH\overset{S}{\overset{\|}{C}}NHR}$$

Since the 1-[2-(N-alkyldithiocarbamoyl)ethyl]-3-alkyl-2-thioureas were easily prepared and easily purified by recrystallization, they appeared to be excellent starting materials for the preparation of 2-mercaptoethylthioureas. Basic hydrolysis removed the dithiocarbamoyl group, but the 2-mercaptoethylthioureas were obtained in impure form. A more satisfactory preparative procedure was to treat the N,S-disubstituted products with silver nitrate in acetonitrile. The N-alkyldithiocarbamoyl function was cleaved by this treatment and the thiourea function was unaffected, the products being one mole of alkyl isothiocyanate and the silver mercaptide of the 2-mercaptoethyl thiourea. This preparation is another example of the metal ion-assisted mercaptan elimination reaction,[8] one in which the mercaptan is the product of interest and not the isothiocyanate. Silver ion could not be eliminated completely from the mercaptide by treatment with hydrogen sulfide, but, when the mercaptide was triturated with a solution of sodium sulfide and sodium hydroxide, silver sulfide was precipitated completely. Acidification of the filtrate gave the 2-mercaptoethylthiourea in relatively pure form. In this manner the 1-alkyl-3-(2-mercaptoethyl)-2-thioureas were prepared in which the alkyl group was methyl, ethyl, isopropyl, n-butyl, and n-heptyl. All but the isopropyl compound were liquids at room temperature.



$$\mathrm{RNH\overset{S}{\overset{\|}{C}}SCH_2CH_2NH\overset{S}{\overset{\|}{C}}NHR \xrightarrow[Et_3N]{AgNO_3} RNCS + Et_3NH^+NO_3^- + AgSCH_2CH_2NH\overset{S}{\overset{\|}{C}}NHR \xrightarrow[NaOH]{Na_2S} NaSCH_2CH_2NH\overset{SNa}{\overset{|}{C}}{=}NR + Ag_2S \xrightarrow{H^+} HSCH_2CH_2NH\overset{S}{\overset{\|}{C}}NHR}$$

When an attempt was made to distil 1-(2-mercaptoethyl)-3-n-butyl-2-thiourea at reduced pressure, material came over at 102–120° (1.5 mm.) and solidified in the receiver. This solid gave an infrared spectrum quire different from that of the thiourea. It appeared that cyclization to 2-n-butylamino-2-thiazoline had occurred, and this was confirmed when the thiazoline was prepared by treating 2-aminoethanol with n-butyl iso-

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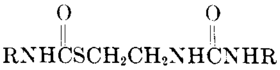
[8] A. F. Ferris and B. A. Schutz, *J. Org. Chem.*, **28**, 71 (1963).

TABLE III

1-[2-(N-ALKYLTHIOLCARBAMOYL)ETHYL]-3-ALKYLUREAS



$\mathrm{RNH}\overset{O}{\overset{\|}{C}}\mathrm{SCH_2CH_2NH}\overset{O}{\overset{\|}{C}}\mathrm{NHR}$

R	Yield, %	M.p., °C.	Calcd. C	Calcd. H	Calcd. N	Calcd. S	Found C	Found H	Found N	Found S
n-C_3H_7	94	138–139	48.55	8.56	16.99	12.96	48.72	8.65	16.72	13.16
n-C_4H_9	82	127.5–130	52.33	9.15	15.26	11.64	52.18	8.98	15.41	11.48
n-$C_{12}H_{25}$	100	129.5–131	67.28	11.50	8.41	6.41	67.16	11.36	8.54	6.60
$C_2H_5O_2CCH_2$	83	131–133.5	42.97	6.31	12.53	9.56	43.08	6.49	12.58	9.40
C_6H_5	96	196.5–200	60.93	5.43	13.32	10.17	60.76	5.58	13.31	10.19

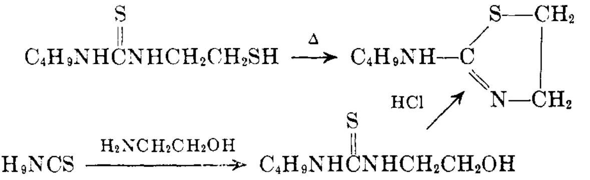
TABLE IV

1-(2-MERCAPTOETHYL)-3-ALKYLUREAS

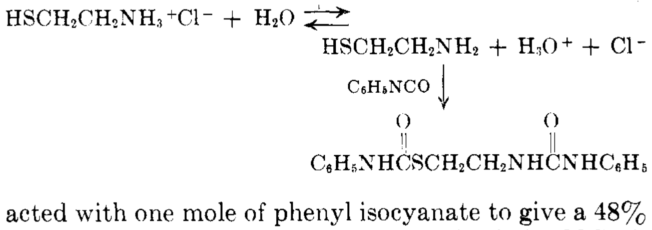
$\mathrm{HSCH_2CH_2NH}\overset{O}{\overset{\|}{C}}\mathrm{NHR}$

R	Yield, %	M.p., °C.	Calcd. C	Calcd. H	Calcd. N	Calcd. S	Found C	Found H	Found N	Found S
n-C_3H_7	87	120–121	44.41	8.70	17.27	19.76	44.58	8.56	17.08	19.83
n-C_4H_9	85	75.5–77	47.69	9.15	15.90	18.19	47.48	9.01	16.06	18.32
n-$C_{12}H_{25}$	79	98–99	62.45	11.18	9.71	11.11	62.24	11.08	9.79	11.22
$C_2H_5O_2CCH_2$	59	85.5–87	40.76	6.84	13.58	15.54	40.69	6.69	13.38	15.70
HO_2CCH_2	71	149.5–150.5	33.70	5.66	15.72	17.99	33.76	5.70	15.83	17.99
C_6H_5	99	141.5–143	55.07	6.16	14.28	16.33	55.18	6.23	14.22	16.19

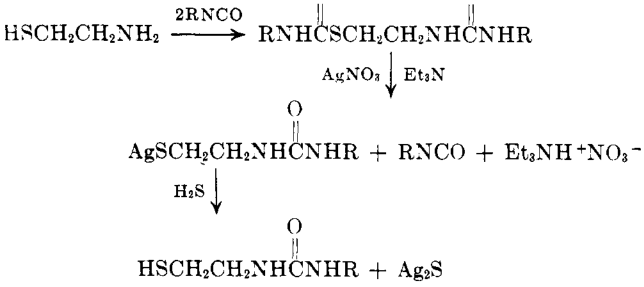
thiocyanate and treating the product with hydrochloric acid. Since most of the 2-mercaptoethylthioureas could not be purified either by crystallization or by distillation, they were characterized as 2,4-dinitrophenyl sulfides (Table II).



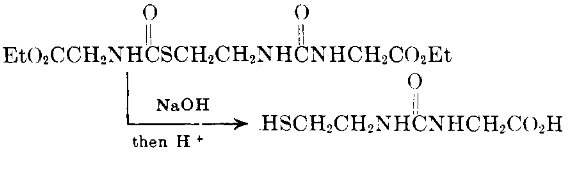
The isocyanates had an even stronger tendency than the isothiocyanates to react at both ends of the 2-mercaptoethylamine molecule. When phenyl isocyanate was added to a suspension of 2-mercaptoethylamine hydrochloride in acetonitrile no reaction took place. When a little water was added the 2-mercaptoethylamine hydrochloride hydrolyzed sufficiently to react, and the N,S-disubstituted product, 1-[2-(N-phenylthiolcarbamoyl)ethyl]-3-phenylurea, was formed, along with some *sym*-diphenylurea from reaction of the isocyanate with water. Free 2-mercaptoethylamine reacted with one mole of phenyl isocyanate to give a 48% yield (based on 2-mercaptoethylamine) of the N,S-disubstituted material as the sole product. With two moles of isocyanate the yield was 96%. When the sodium salt of 2-mercaptoethylamine reacted with the isocyanate, the disubstituted compound was again the principal product, but a 34% yield of 1-(2-mercaptoethyl)-3-phenylurea was obtained also. A better route to the mercaptoethylurea (99% yield) was cleavage of 1-[2-(N-phenylthiolcarbamoyl)ethyl]-3-phenylurea with silver nitrate, followed by treatment of the silver mercaptide with aqueous sodium sulfide or alcoholic hydrogen sulfide.



Extension of this reaction to other isocyanates provided a very general route to 1-(2-mercaptoethyl)-3-alkylureas. Reaction of 2-mercaptoethylamine with two moles of isocyanate, followed by cleavage of the N,S-disubstituted product with silver nitrate or mercuric chloride and treatment of the mercaptide with sulfide gave good yields of mercaptoethylureas.



The N,S-disubstituted compounds from *n*-propyl, *n*-butyl, and *n*-dodecyl isocyanates and from ethyl isocyanatoacetate were prepared, and all were cleaved to the corresponding mercaptoethylureas by the metal ion-assisted reaction. In addition, 1-[2-(N-ethoxycarbonylmethylthiolcarbamoyl)ethyl]-3-ethoxycarbonylmethylurea was hydrolyzed directly to 1-(2-mercaptoethyl)-3-carboxymethylurea in 71% yield by treatment with aqueous base. Recently 1-(2-mercaptoethyl)-3-methylurea has been prepared by treating cystamine (the disulfide of 2-mercaptoethylamine) with methyl isocyanate and subjecting the prod-



uct to electrolytic reduction.[9] Unless equipment for such reduction is readily available, the technique here described will be found more convenient. Properties of the 1-[2-(N-alkylthiolcarbamoyl)ethyl]-3-alkylureas are summarized in Table III, and those of the 1-(2-mercaptoethyl)-3-alkylureas in Table IV.

Experimental[10]

S-(2-Aminoethyl) N-Phenyldithiocarbamate Hydrochloride.—To a solution of 12.5 g. (0.11 mole) of 2-mercaptoethylamine hydrochloride in 100 ml. of 95% ethanol (pH 5.5) was added 13.5 g. (0.10 mole) of phenyl isothiocyanate at 23°. There was no apparent reaction. When 5 drops of 10% sodium hydroxide solution was added (pH 6) the temperature began to rise. At 38° solid began to precipitate, and at 40° the mixture set up solid. After 2 hr. the temperature had fallen back to room temperature. An additional 50 ml. of ethanol was added, and the solid was recovered by suction filtration. Cooling the filtrate in ice brought down more solid, also recovered by suction filtration. The solids were combined and dried in air. The crude S-(2-aminoethyl) N-phenyldithiocarbamate hydrochloride thus recovered amounted to 17.9 g. (72%) and melted at 155–162°. The solid was recrystallized twice from 95% ethanol to give pure product, m.p. 160–164° dec.

Anal. Calcd. for $C_9H_{13}N_2S_2Cl$: C, 43.45; H, 5.27; N, 11.26; S, 25.77. Found: C, 43.23; H, 5.20; N, 11.18; S, 25.91.

S-(2-Aminoethyl) N-*n*-Butyldithiocarbamate Hydrochloride.—2-Mercaptoethylamine hydrochloride (12.5 g., 0.11 mole) and 11.5 g. (0.10 mole) of *n*-butyl isothiocyanate reacted as described previously to give 17.0 g. (74%) of S-(2-aminoethyl) N-*n*-butyldithiocarbamate hydrochloride, m.p. 151–155°. Two recrystallizations from absolute ethanol gave pure product, m.p. 153–156°.

Anal. Calcd. for $C_7H_{17}N_2S_2Cl$: C, 36.74; H, 7.49; N, 12.25; S, 28.02; Cl, 15.50. Found: C, 36.77; H, 7.57; N, 12.24; S, 28.13; Cl, 15.38.

S-(2-Dimethylamino)ethyl N-Phenyldithiocarbamate.—2-(Dimethylamino)ethyl mercaptan hydrochloride (7.1 g., 0.05 mole) and 6.8 g. (0.05 mole) of phenyl isothiocyanate reacted as described previously, and the reaction mixture was poured into 200 ml. of ice water. When the mixture was made strongly basic a solid separated. After recovery and drying it amounted to 7.9 g. (66%), m.p. 109–113°. Two recrystallizations from 95% ethanol gave 4.9 g. of pure S-(2-dimethylamino)ethyl N-phenyldithiocarbamate, m.p. 110.5–112.5°.

Anal. Calcd. for $C_{11}H_{16}N_2S_2$: C, 54.96; H, 6.71; N, 11.66; S, 26.67. Found: C, 54.82; H, 6.76; N, 11.87; S, 26.46.

1-(2-Mercaptoethyl)-3-phenyl-2-thiourea.—To a solution of 6.8 g. (0.06 mole) of 2-mercaptoethylamine hydrochloride in 35 ml. of 95% ethanol was added a solution of 2.4 g. (0.06 mole) of sodium hydroxide in 4 ml. of water. Sodium chloride precipitated. To this mixture at 23° was added 6.8 g. (0.05 mole) of phenyl isothiocyanate. The temperature rose rapidly to 39°, then dropped slowly. After 2 hr. the reaction mixture was poured into 200 ml. of ice water, and a solid separated. After recovery by suction filtration and drying *in vacuo* the crude 1-(2-mercaptoethyl)-3-phenyl-2-thiourea amounted to 9.7 g. (91%), m.p. 105–114°. Two recrystallizations from 95% ethanol raised the melting point to 113–116.5°.

Anal. Calcd. for $C_9H_{12}N_2S_2$: C, 50.91; H, 5.70; N, 13.20; S, 30.20. Found: C, 50.74; H, 5.60; N, 13.41; S, 30.48.

1-[2-(N-*n*-Butyldithiocarbamoyl)ethyl]-3-*n*-butyl-2-thiourea.—To a suspension of 11.4 g. (0.10 mole) of 2-mercaptoethylamine hydrochloride in 25 ml. of 95% ethanol was added a solution of 4.0 g. (0.10 mole) of sodium hydroxide in 5 ml. of water. A new solid came out of solution. To this mixture was then added 23.1 g. (0.2 mole) of *n*-butyl isothiocyanate. The temperature rose rapidly from 33° to 75°, then dropped back to 30° over about an hour. The reaction mixture was then poured into 400 ml. of ice water. The solid which separated was recovered by suction filtration and dried *in vacuo*. The crude 1-[2-(N-*n*-butyldithiocarbamoyl)ethyl]-3-*n*-butyl-2-thiourea amounted to 30.8 g. (100%). The entire sample was recrystallized from 150 ml. of acetonitrile to give 17.5 g. of purified material, m.p. 98–101.5°. A second recrystallization of a portion from acetonitrile did not change the melting point.

Anal. Calcd. for $C_{12}H_{25}N_3S_3$: C, 46.87; H, 8.19; N, 13.66; S, 31.28. Found: C, 47.02; H, 8.10; N, 13.57; S, 31.46.

1-(2-Mercaptoethyl)-3-*n*-butyl-2-thiourea.—To a solution of 55.4 g. (0.18 mole) of 1-[2-(N-*n*-butyldithiocarbamoyl)ethyl]-3-*n*-butyl-2-thiourea in 250 ml. of acetonitrile was added 18.2 g. (0.18 mole) of triethylamine and, with vigorous stirring, a solution of 30.6 g. (0.18 mole) of silver nitrate in 75 ml. of acetonitrile. The gray-brown silver derivative which separated was recovered by suction filtration and washed with acetonitrile. The damp solid was triturated with a solution of 60.1 g. (0.25 mole) of sodium sulfide nonahydrate to which 100 ml. of 10% sodium hydroxide solution had been added. The black silver sulfide which was formed was removed by filtration and washed with water. A yellow oil separated when the filtrate was made acid with 5 *N* hydrochloric acid, and was extracted into two 200-ml. portions of ether. The ether solution was dried over anhydrous magnesium sulfate, and on evaporation left 16.4 g. (47%) of yellow liquid 1-(2-mercaptoethyl)-3-*n*-butyl-2-thiourea.

An attempt was made to distil a 5.5-g. sample of the crude thiourea at reduced pressure. At 1.5 mm. and a pot temperature of 150–170°, material distilled at 102–120° (1.5 mm.) and solidified in the receiver. There was obtained 2.5 g. of white solid, m.p. 61–66°. The infrared spectrum of this material was identical to that of 2-*n*-butylamino-2-thiazoline. Yield of thiazoline produced in this pyrolysis was 55%.

To a solution of 1.9 g. (0.01 mole) of crude thiourea in 25 ml. of 95% ethanol was added 4 ml. of 10% sodium hydroxide solution (0.01 mole) and a solution of 2.0 g. (0.01 mole) of 1-chloro-2,4-dinitrobenzene in 35 ml. of ethanol. The solution was heated to boiling and filtered hot, and on cooling deposited a yellow solid. The 2,4-dinitrophenyl sulfide derivative of 1-(2-mercaptoethyl)-3-*n*-butyl-2-thiourea amounted to 2.5 g. (69%). m.p. 135–137°. Two recrystallizations from 95% ethanol gave purified solid, m.p. 135–137°.

Anal. Calcd. for $C_{13}H_{18}O_4N_4S_2$: C, 43.56; H, 5.06; N, 15.63; S, 17.89. Found: C, 43.66; H, 4.88; N, 15.50; S, 18.00.

2-*n*-Butylamino-2-thiazoline.—To a solution of 9.2 g. (0.15 mole) of 2-aminoethanol in 50 ml. of 95% ethanol was added slowly 17.3 g. (0.15 mole) of *n*-butyl isothiocyanate. The temperature was held at 30–45° by cooling. After standing 3 hr., the reaction mixture was poured into 300 ml. of ice–water, and an oil separated. The oil was extracted into two 100-ml. portions of ether, and the ether solution was dried over anhydrous magnesium sulfate. Evaporation of the ether left 21.3 g. (81%) of crude 1-*n*-butyl-3-(2-hydroxyethyl)-2-thiourea.

To the crude thiourea (0.077 mole) was added 66 ml. (0.77 mole) of concentrated hydrochloric acid, and the resulting homogeneous solution was heated under reflux for 7 hr. The solution was cooled in ice and made strongly basic with a solution of 35 g. of sodium hydroxide in 50 ml. of water. A white solid separated and was recovered by suction filtration and dried. The crude 2-*n*-butylamino-2-thiazoline amounted to 17.2 g. (90%) and melted at 64–67.5°. A sample recrystallized from 1:1 ethanol-water melted at 67–69°.

Anal. Calcd. for $C_7H_{14}N_2S$: C, 53.12; H, 8.92; N, 17.71; S, 20.26. Found: C, 52.97; H, 8.96; N, 17.83; S, 19.99.

Rearrangement of S-(2-Aminoethyl) N-Phenyldithiocarbamate Hydrochloride.—In 50 ml. of anhydrous acetonitrile was suspended 7.5 g. (0.03 mole) of S-(2 aminoethyl) N-phenyldithiocarbamate hydrochloride, and 4.0 g. (0.04 mole) of triethylamine was added. On trituration all the solid went into solution, and a new solid crystallized. After 2 hr. the mixture was poured into 300 ml. of water, and an oil separated and crystallized. After recovery and drying the solid amounted to 4.9 g. (77%), m.p. 111.5–114°. Its infrared spectrum was identical with that of an authentic sample of 1-(2-mercaptoethyl)-3-phenyl-2 thiourea.

1-(2-Mercaptoethyl)-3-isopropyl-2-thiourea.—The procedure for 1-(2-mercaptoethyl)-3-*n*-butyl-2-thourea was followed with 28.0 g. (0.10 mole) of 1-[2-(isopropyldithiocarbamoyl)ethyl]-3-isopropyl-3-thiourea, 17.0 g. (0.10 mole) of silver nitrate, 10.1 g. (0.10 mole) of triethylamine, and 28.8 g. (0.12 mole) of sodium sulfide nonahydrate. There was obtained 12.6 g. (71%) of crude 1-(2-mercaptoethyl)-3-isopropyl-2-thiourea, m.p. 102–103°. Two recrystallizations from 95% ethanol gave pure material, m.p. 102–103.5°.

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[9] K. Schimmelschmidt, H. Hoffmann, and E. Mundlos, *Ber.*, **96**, 38 (1963).

[10] All melting points are corrected and boiling points are uncorrected. Microanalyses by Galbraith Laboratories, Knoxville, Tennessee.

Anal. Calcd. for $C_6H_{14}N_2S_2$: C, 40.41; H, 7.91; N, 15.71; S, 35.96. Found: C, 40.58; H, 7.94; N, 15.79; S, 36.17.

1-[2-(N-Phenylthiolcarbamoyl)ethyl]-3-phenylurea.—To a suspension of 6.8 g. (0.05 mole) of 2-mercaptoethylamine hydrochloride in 50 ml. of acetonitrile was added 5.1 g. (0.05 mole) of triethylamine. A new solid came out of solution. To the resulting suspension was added 6.0 g. (0.05 mole) of phenyl isocyanate. The temperature rose rapidly from 25° to 53°, then dropped back to 25° over about 90 min. The reaction mixture was poured into 200 ml. of ice water and a solid separated. After recovery by suction filtration and drying, the 1-[2-(N-phenylthiolcarbamoyl)-ethyl]-3-phenylurea amounted to 7.6 g. (96%), m.p. 165–189°. A portion of this solid was recrystallized three times from 95% ethanol to give material melting at 196.5–200°.

Anal. Calcd. for $C_{16}H_{17}O_2N_3S$: C, 60.93; H, 5.43; N, 13.32; S, 10.17. Found: C, 60.76; H, 5.58; N, 13.31; S, 10.19.

1-(2-Mercaptoethyl)-3-phenylurea.—In a solution of 4.6 g. (0.0457 mole) of triethylamine in 75 ml. of acetonitrile was suspended 14.4 g. (0.0457 mole) of 1-[2-(N-phenylthiolcarbamoyl)-ethyl]-3-phenylurea. To the suspension was added a solution of 7.8 g. (0.0457 mole) of silver nitrate in 25 ml. of acetonitrile. The mixture was triturated for an hour, an intense odor of phenyl isocyanate becoming apparent. The pH at this point was about six. When 2 ml. of triethylamine was added, bringing the pH to 7.5, the isocyanate odor rapidly disappeared.

The solid silver mercaptide was recovered by suction filtration and washed with 25 ml. of acetonitrile. While still damp it was added to a solution of 18.0 g. (0.075 mole) of sodium sulfide nonahydrate in 75 ml. of water. Black silver sulfide appeared rapidly when the mixture was triturated. When conversion appeared to be complete, the silver sulfide was recovered by suction filtration, washed with 25 ml. of water, and air-dried. The aqueous filtrate was made strongly acid with 5 *N* hydrochloric acid, and a copious cream colored precipitate came down. This was recovered by suction filtration, washed with 25 ml. of water, and air-dried. The acetonitrile filtrate from the original reaction was poured into 300 ml. of water, and a white solid, presumably byproduct 1,3-diphenylurea, came out. It was recovered by suction filtration and dried.

The silver sulfide recovered amounted to 6.2 g. (theory 5.7 g.). The by-product 1,3-diphenylurea amounted to 3.7 g. (77%), m.p. 221–228°. After recrystallization from ethanol it melted at 236–243°. The crude 1-(2-mercaptoethyl)-3-phenylurea amounted to 8.9 g. (99%). Recrystallization from 75 ml. of ethanol gave 7.2 g. of relatively pure material, m.p. 141–143°. Two more recrystallizations from ethanol gave an analytical sample, m.p. 141.5–143°.

Anal. Calcd. for $C_9H_{12}ON_2S$: C, 55.07; H, 6.16; N, 14.28; S, 16.33. Found: C, 55.18; H, 6.23; N, 14.22; S, 16.19.

1-(2-Mercaptoethyl)-3-carboxymethylurea.—To 16.8 g. (0.05 mole) of 1-[2-(N-ethoxycarbonylmethylthiolcarbamoyl)ethyl]-3-ethoxycarbonylmethylurea was added 80 ml. of 10% sodium hydroxide solution (0.20 mole). The solid went into solution rapidly, and the solution became warm. After an hour the solution was filtered and cooled in ice, and 40 ml. of 5 *N* hydrochloric acid was added slowly. Gas evolved vigorously, and a solid crystallized. It was recovered by suction filtration and dried in a vacuum oven. The crude 1-(2-mercaptoethyl)-3-carboxymethylurea amounted to 6.3 g. (71%), m.p. 143–147°. The crude product was dissolved in 60 ml. of hot ethanol, and the solution was filtered to remove a small amount of sodium chloride. Cooling brought down 3.7 g. of purified urea, m.p. 147–149°. A portion was recrystallized a second time from ethanol to give an analytical sample, m.p. 149.5–150.5°.

Anal. Calcd. for $C_5H_{10}O_3N_2S$: C, 33.70; H, 5.66; N, 15.72; S, 17.99. Found: C, 33.76; H, 5.70; N, 15.83; S, 17.99.

The Dealkylation of Aromatic Amines

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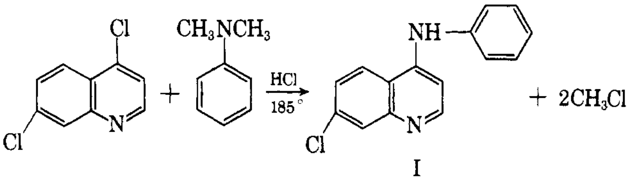
Received April 22, 1963

Tertiary aromatic amines were dealkylated smoothly to secondary aromatic amines at about 150° by passing hydrogen bromide through the molten salt. Secondary aromatic amines were converted to anilines at about 200°. All the rates followed pseudo first-order kinetics which made possible a comparative study among a number of tertiary amines under varying conditions.

We observed the rather unusual results of an attempted Friedel-Crafts reaction. *para* Substitution in dimethylaniline was anticipated but instead the product I was isolated in good yield. Obviously a dealkylation had occurred prior to the coupling process, and this paper reports our study of the dealkylation process.



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Many methods of dealkylation are available.[3-11] Only a few methods deal with the direct action of a mineral acid on an alkylamine,[12] stemming mainly from the work of Hickinbottom,[13,14] who found that N-methylaniline, heated in a slow stream of hydrogen chloride, yields aniline. Monoalkylaniline hydrobromides decompose between 250–300° with the elimination of the alkyl group as olefin and alkyl bromide. Tertiary alkyl groups are removed readily by acids at 110-140°.[15] Treatment of N-methylaniline under Zeisel conditions results in a yield of only 3% methyl iodide. N-Butylaniline is unaffected by 19 *N* sulfuric acid at 140° for 30 hours. An interesting application

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(1) Abstracted from the Ph.D. thesis of R. A. C., National Defense Education Act Fellow, 1959–1962.

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(11) Zinc or cobalt halides: C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 615–618.

(12) The Hofmann–Martius rearrangement[11] concerns the direct action of a mineral acid, but, since it is carried out in a sealed tube at a high temperature and involves rearrangement, it is not included in the discussion.

(13) W. J. Hickinbottom, "Reactions of Organic Compounds," Longmans Green and Co., New York, N. Y., 1948, p. 306.

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